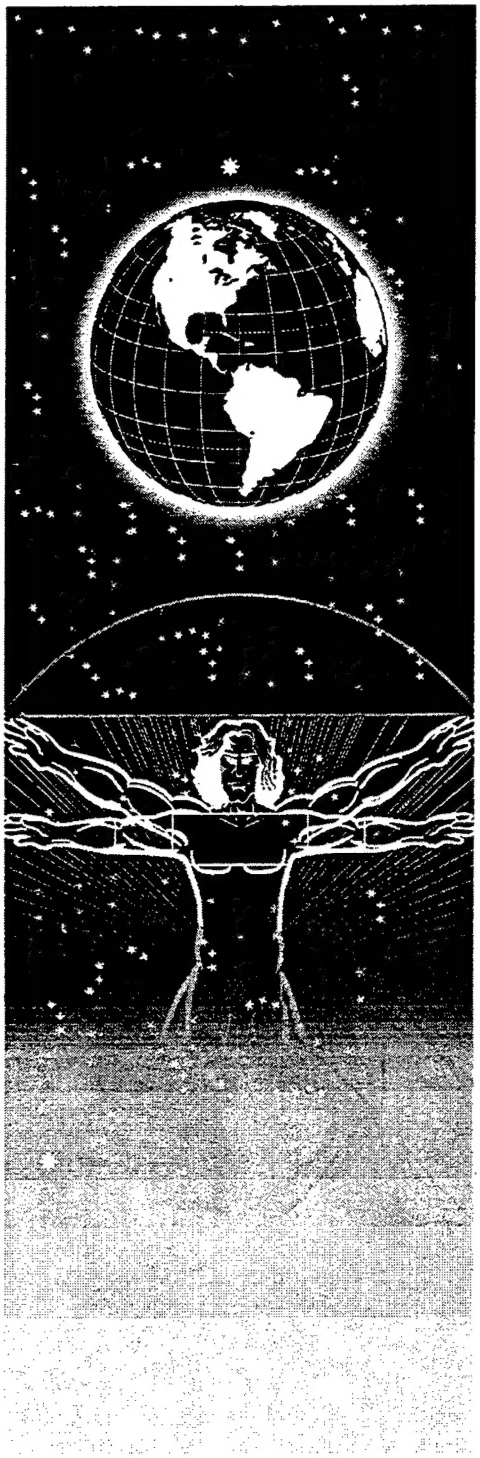
AL/CF-TR-1997-0030



UNITED STATES AIR FORCE
ARMSTRONG LABORATORY

Survival Models for Predicting Altitude Decompression Sickness

Nandini Kannan
Apaarna Raychaudhuri

University of Texas at San Antonio
Division of Mathematics and Statistics
6900 N. Loop, 1604 West
San Antonio, Texas 78249

January 1998

Approved for public release;

distribution is unlimited.

Crew Systems Directorate
Crew Technology Division
2504 Gillingham Dr STE 25
Brooks AFB, TX 78235-5104

NOTICES

This final technical report was submitted by personnel of the Systems Research Branch, Crew Technology Division, Armstrong Laboratory, AFMC, Brooks Air Force Base, Texas under job order 7184-58-01.

When Government drawings, specifications, or other data are used for any purpose other than in connection with a definitely Government-related procurement, the United States Government incurs no responsibility or any obligation whatsoever. The fact that the Government may have formulated or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication, or otherwise in any manner construed, as licensing the holder or any other person or corporation; or as conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

The mention of trade names or commercial products in this publication is for illustration purposes and does not constitute endorsement or recommendation for use by the United State Air Force.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

Government agencies and their contractors registered with Defense Technical Information Center (DTIC) should direct requests for copies to: Defense Technical Information Center, 8725 John J. Kingman Rd., STE 0944, Ft. Belvoir, VA 22060-6218.

Non-Government agencies may purchase copies of this report from: National Technical Information Services (NTIS), 5285 Port Royal Road, Springfield, VA 22161-2103.

F. WESLEY BAUMGARDNER, Ph.D.
Chief, Systems Research Branch

ROGER L. STORK, Colonel, USAF, BSC
Chief, Crew Technology Division

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	January 1998	Final, January - July 1996

4. TITLE AND SUBTITLE
Survival Models for Predicting Altitude Decompression Sickness

5. FUNDING NUMBERS
PE: 62202F
PR: 7184
TA: 58
WU: 01

6. AUTHOR(S)
Nandini Kannan
Apaarna Raychaudhuri

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Texas at San Antonio
Division of Mathematics and Statistics
6900 N. Loop, 1604 West
San Antonio, TX 78249

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Armstrong Laboratory
Crew Systems Directorate
Crew Technology Division
2504 Gillingham Dr STE 25
Brooks Air Force Base TX 78235-5104

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
AL/CF-TR-1997-0030

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Survival Analysis methods have been used to model the onset of Decompression Sickness (DCS) which occurs routinely as a result of high altitude exposure. Both parametric and nonparametric models were developed. These models were used to predict the risk of DCS for different flight profiles. The risk factors that have a significant effect on the risk of DCS were also identified. Cross validation techniques are provided to examine the goodness of fit of the model. The loglogistic model was modified to incorporate data on bubble grades and times.

14. SUBJECT TERMS
Decompression sickness
Survival analysis

15. NUMBER OF PAGES
42

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

THIS PAGE INTENTIONALLY LEFT BLANK

Table of Contents

List of Tables

List of Figures

Acknowledgments

The authors would like to thank Dr. Andrew A. Pilmanis, Lt. Zahid Sulaiman, and other scientific staff of the High Altitude Protection Function, Armstrong Laboratory, Brooks AFB. We also appreciate the assistance provided by Dr. James T. Webb and Mr. Lambros Petropoulus of Krug Life Sciences.

1. Introduction

Exposure to significant changes in environmental pressure can cause decompression sickness (DCS). These situations are encountered during diving, high altitude exposures or artificially induced pressure changes in hyperbaric or hypobaric chambers. For large and sufficiently rapid pressure reductions, supersaturation occurs as a result of the inability of tissue gas exchange processes to expel excess nitrogen. These gases which come out of solution when tissues are sufficiently supersaturated collect as bubbles in the tissue. The size and location of these bubbles are thought to have a significant effect on the resulting symptoms of DCS. The risks can be decreased or prevented with sufficient denitrogenation by prebreathing pure oxygen before such exposures.

The risk of DCS increases with extended exposure times, very high altitudes, and level of physical activity required during the exposure. The assessment of DCS risk for both civilian and military personnel under specified flight protocols is a critical problem that the USAF deals with on a regular basis. To provide answers to these questions, and also to obtain a clearer understanding of the effects of denitrogenation, the Armstrong Laboratory has been working on an approporiate model to predict DCS risk using physical and physiological principles.

The AL/ CFTS High Altitude Protection Function at the Armstrong Laboratory has conducted experiments on human subjects in a hypobaric chamber for the past several years. The subjects were exposed to different altitudes, varying denitrogenation times, and different prebreathing mixtures. The subjects were monitored continuously and were required to report any unusual pain or other symptoms. If the symptoms were indicative of DCS, the experiment was terminated with the subject being brought down to ground level. Several measurements were recorded during the experiment including onset time of DCS, physical activity, time spent in the chamber etc. The data collected also included a measure of bubble grade measured on a Spencer scale using echocardiography.

There has been extensive research in the literature to model decompression sickness based on experimental data. Most of the available literature, however, has dealt with diving data. These models cannot be adjusted to work for altitude exposures because of the unique characteristics that are encountered. A significant

difference is the faster ascent rate in high altitude situations compared to the slower ascent rates for divers. There is also a possibility of instantaneous pressure loss in aircraft.

Most research on altitude DCS modeling has focused on mathematical models describing bubble growth. Van Liew et al. [1] developed a probabilistic model of altitude DCS. The mechanistic principles used in the model were based on the premise that the risk of DCS is related to the number of bubbles and the volume of gas that can be liberated from a unit of tissue. The authors developed equations that incorporated these premises, and used these equations in the risk function. They tested several models to determine the one that best fit the data. The covariates (risk factors) used in the model were duration of 100% O_2 at ground level (prebreathing), atmospheric pressure after ascent, and exposure duration.

Gerth and Vann [2] developed an extensive model for bubble dynamics to provide an assessment of DCS. The bubble dynamic equations were similar to those in Van Liew et al. In the report, the percentage of individuals with DCS was used as the response variable and maximum likelihood methods used to estimate the model parameters. In an appendix, the authors discussed the need for including onset times to improve the predictions from the model.

The description of bubble growth tends to be rather complicated by the numerous underlying physical processes. Several assumptions have to be made in order to obtain a numerical soultion, which can lead to erroneous results. In addition, most authors ignored the time to onset of DCS in the model. These models based on bubble growth provided limited insight into the effects of different covariates on the risk of DCS.

Since the occurrence of DCS is a random event that is affected by factors like prebreathing, exercise, and exposure time, statistical techniques seem to be appropriate. Kumar and others recognized that survival analysis techniques should be a part of any attempt to model DCS risk. In a series of papers, these authors explored different statistical models.

Kumar et al [3] used logistic regression to model the percentage of DCS in hypobaric chamber training data. They showed that with zero prebreathing, moderate exposure times, and simulated extravehicular activities (EVA), the threshold for occurrence of DCS symtoms was 502 mm Hg pressure (11,000 ft.); while with zero

prebreathing, shorter exposure times and knee bending exercise, the threshold for symptoms is around 270 mm Hg pressure (26,000 ft).

In a later article, Kumar et al. [4] evaluated the effect of circulating microbubbles (CMB) on the incidence of DCS using Cox's Proportional Hazard model. They observed that the risk of DCS is significantly higher in the presence of CMB. It was also shown that the risk is lower for individuals with late onset of CMB.

Kumar and Powell [5] were the first to include the actual onset times in a survival model. The risk factors considered were Tissue Ratio (TR), a measure of tissue nitrogen decompression stress and CMB status. The models used the logarithm of time to DCS and maximum likelihood techniques to estimate the model parameters. In a recent article, Conkin et al. [6] used loglogistic survival models on the data from 66 NASA and USAF hypobaric chamber tests. The models examined the effect of TR and exercise status (yes, no) on the incidence of DCS.

The survey of current literature in the area of altitude DCS shows the limitations of the models that are currently in use. There is clearly a need for a comprehensive model that includes the time to onset of DCS, the flight conditions, and data on bubbles. This model should also help to identify the primary risk factors. This report is an attempt to develop statistical models using survival analysis techniques. Predictions from the model will be compared to empirical data to evaluate the effectiveness and validity of the approach.

In the next section, we introduce the reader to the basic concepts of survival analysis. Section 3 describes the database, and preliminary exploratory data analysis. In Section 4, survival models are devloped and used for predictions. Section 5 provides conclusions and suggestions for future research.

2. Survival Analysis

Survival Analysis refers to a collection of statistical techniques used to analyze the lifetime or failure time of individuals or components. Examples include the time to remission of a disease, time to failure of an electrical component, or time to death of a biological unit. The major applications of survival analysis techniques have been in the engineering and biomedical sciences.

Most of the early work in survival analysis focused on finding appropriate models to describe the survival time, the time to occurrence of a disease/symptom. However, in recent years there has been substantial interest in the identification of risk factors related to the development of the disease. The survival probability may be increased by controlling the levels of these risk factors.

Let T denote the time to onset of DCS. This is the "survival time", which is a non-negative random variable. The behavior of this random variable can be specified in terms of its probability distribution using any one of the functions described below.

The survival function is defined as

$$S(t) = P(T > t),$$

i.e., the probability that the individual does not exhibit any symptoms of DCS up to time t. The survival function is a nonincreasing (decreasing) function of time t with the properties that

$$S(0) = 1, \qquad S(\infty) = 0,$$

i.e., the probability of being symptom free for an infinite time is zero. The survival function is also known as the cumulative survival rate.

The Cumulative Distribution Function (Cdf) is defined as

$$F(t) = P(T \leq t) = 1 - S(t),$$

the probability that DCS symptoms occur before time t. Clearly, the cdf starts at 0 and increases to 1. A steep cdf indicates the rate of survival is low or that onset time is relatively quick. A gradual, slow rising graph indicates the time to onset is higher. Graphs of the cdf are useful to compare the performances of individuals with different flight profiles. The survival function or cdf can be estimated from the data very easily using,

$$\hat{F}(t) = \frac{\text{No. of individuals with onset times less than } t}{\text{total no. of individuals}}.$$

The probability density function (pdf) $f(t)$ of the survival/onset time T is defined as the probability that an individual exhibits DCS symptoms in a small interval per unit time. The usual relation between the cdf and the pdf is:

$$F(t) = \int_0^t f(x)dx.$$

The survival time T is modeled using various forms of the density function. The common survival models include the exponential, gamma, Weibull, lognormal, and loglogistic. Each pdf has its unique functional form, and defines a corresponding survival function and cdf. The density functions are usually characterized by parameters, in most cases these are location and scale parameters. The choice of an appropriate distribution depends on the underlying characteristics of the data.

The hazard or risk function $r(t)$ specifies the instantaneous rate of developing symptoms at time t, given that the individual is symptom free until t. Therefore $r(t)$ can be interpreted as the conditional failure rate. The risk function is appealing since the function describes the way in which the instantaneous risk of DCS changes with time in the chamber. The risk function is defined as

$$r(t) = \frac{f(t)}{S(t)}$$

where $f(t)$ is the probability density function of the onset time.

The risk function changes according to the underlying survival distribution. If the underlying distribution is exponential, the risk function is a constant over time. This essentially says that the risk of DCS remains constant, irrespective of the time spent at altitude. This is not a reasonable assumption for modeling onset of DCS, as risk should increase over time. Risk functions can also be increasing or decreasing. Survival distributions are then classified as IFR (increasing failure rate) or DFR (decreasing failure rate). The gamma and Weibull models belong to these classes for appropriate choices of parameters. For DCS modeling, IFR distributions are obvious candidates. However, from empirical evidence, it is known that the risk of DCS initially increases up to a certain time point, and then decreases because of

denitrogenation. It is therefore appropriate to consider the "inverted bathtub" forms of the risk function. Distributions in this class are the loglogistic and the lognormal.

Another characteristic unique to survival data is the notion of "censoring". In the Air Force Study, the moment the subject experiences any symptoms, the experiment is aborted and the subject brought down to ground level. However, individuals who do not report any symptoms will remain in the chamber until the duration of the flight profile. They could have experienced symptoms of DCS if the flight duration were increased. This is the definition of censoring in survival literature. For individuals who experience DCS, the time to onset of DCS is available. For other subjects, the time to DCS is considered to be beyond the duration of the experiment. This is referred to as right censoring.

2.1 Parametric and Nonparametric Models

We now discuss both parametric and nonparametric methods for modeling the survival times. The parametric approach assumes that the survival time has a known distribution which depends on a vector of risk factors $\boldsymbol{x}$. Common models include the exponential, gamma, Weibull, loglogistic, and lognormal. The likelihood involves both censored and uncensored observations. Estimates of the parameters in the model are obtained using maximum likelihood techniques.

The nonparametric approach does not assume any functional form for the underlying survival distribution. This approach uses the Cox type regression models to describe the risk of DCS as a function of $\boldsymbol{x}$. The Proportional hazards model developed by Cox [7] uses the risk function as a dependent variable. It possesses the property that the ratio of the hazard functions of two individuals with covariates x_1 and x_2 does not vary with time. The Cox model may be written as

$$r(t|\boldsymbol{x}) = r_0(t)exp(\boldsymbol{x}'\beta)$$

where $r_0(t)$ is called the baseline hazard, β is a vector of unknown parameters to be estimated, and $\boldsymbol{x}$ is a vector of covariates. The model can be written as

$$\log\left[\frac{r(t)}{r_0(t)}\right] = \boldsymbol{x}'\boldsymbol{\beta}$$

which is a multiple regression model. This allows us to use stepwise regression techniques to determine the risk factors that are of primary importance. The survival function can be expressed as

$$S(t) = [S_0(t)]^{exp(\beta_0+\beta_1 x_1+...\beta_k x_k)}$$

where $S_0(t)$ is the baseline survival function.

For a comprehensive treatment of survival analysis the reader is referred to Lee [8] or Lawless [9]. These references also include details of the parametric and nonparametric approaches.

3. Data Management

This section provides information on the steps taken to generate the dataset used in the statistical analysis. The data collected by the Armstrong Laboratory was provided in the form of two data files. The first file contained the Man Flight Number, Record of Time and Grades of bubbles observed, and Onset time of DCS. The second file contained Man flight number, Flight profile, and the exercise code. A Fortran program was used to extract the information on the manflight number and onset time from the first file. This file contained 1534 records.

In the second file, the flight profiles were replaced by their corresponding pressure, prebreathing time, and time at altitude. This file contained 1693 records. The two data files were merged, with duplicate records being deleted. Records with incomplete information were also removed from the database. This resulted in a sample of $1693 - 159 - 121 = 1413$ observations. The record with the missing flight profile (30 C) was later completed. This resulted in a total sample size of 1414. Man flight number 94206 had no flight profile data, this partial information was later added. Also, before the preparation of this report, data on 12 more subjects was made available, increasing the final sample size to 1426.

Three records in the database had negative onset times. Two individuals reported symptoms almost 24 hours after the flight ended. The onset time for these individuals (83028, 85125) was taken to be the time at altitude. These individuals were not considered to be censored observations since they did exhibit symptoms at some stage. The third individual (90005) reported symptoms just before reaching maximum altitude. This individual was given an onset time of 1 minute.

3.1 Summary of data

Subjects were exposed to high altitudes in a hypobaric chamber for specified time intervals. They were monitored closely for any symptoms of DCS. The data collected included the exercise codes (limb movements in the chamber), time of prebreathing, pressure, time at maximum altitude, and time to onset of DCS symptoms. Doppler ultrasound was used to monitor the formation of microbubbles. The density

of bubbles was recorded according to a Spencer scale (1:low, 4:high) at approximately 15 minute intervals.

The following abbreviations will be used in the report.

ID :	man flight number
PRES:	final pressure (mm Hg)
BR :	prebreathing time (min)
TALT :	time at maximum altitude (min)
EXER :	Exercise Code
ONSET :	time of onset of DCS (min)
CENSOR :	censoring variable (0: no DCS, 1:DCS)
MAXB :	maximum bubble grade
MAXT:	time of onset of maximum bubble grade (min)

Individuals who did not exhibit DCS symptoms were assigned an onset time of 0 in the original database. These censored individuals had their onset time replaced by their corresponding TALT times for the statistical analysis. The data set contained 906 censored observations (incidence rate of 63.5 %).

Several cross classification tables are provided to obtain insight on the characteristics of the data. The first table (Table 3.1) shows a cross classification of subjects by prebreathing time and status of DCS. The percentage of DCS at each level of prebreathing seems to indicate that the incidence of DCS increases with higher prebreathing times. This observation is clearly contradictory to empirical information that denitrogenation reduces the risk of DCS significantly.

In Table 3.2. we present the cross classification of prebreathing times by time at maximum altitude. The maximum prebreathing time for flights of longer duration was 60 minutes. Subjects who prebreathed for extended times of 90, 135 and 240 minutes were only exposed to flight times of 240 minutes.

An examination of a cross classification table of prebreathing time by pressure, seemed to indicate that subjects who prebreathed longer were exposed to higher altitudes and longer flight durations. This suggested modifying the prebreathing times to reflect the underlying exposure time. A new variable was created which was the ratio of prebreathing time to time at maximum altitude (BRTALT) and was used in the subsequent analysis.

Table 3.1 Classification of BR by CENSOR

	CENSOR		
BR (min)	0	1	Total
0	482	53	535
15	8	15	23
60	287	323	610
75	56	71	127
90	8	5	13
135	65	51	116
240	2	0	2
Total	908	518	1426

Table 3.2 Classification of BR by TALT

	TALT (min)					
BR (min)	120	180	240	360	480	Total
0	0	0	19	474	42	535
15	0	0	23	0	0	23
60	4	75	272	50	209	610
75	0	25	102	0	0	127
90	0	0	13	0	0	13
135	0	0	116	0	0	116
240	0	0	2	0	0	2
Total	4	100	547	524	251	1426

Table 3.3 Classification of EX by CENSOR

	CENSOR		
EX	0	1	Total
1	82	47	129
2	825	467	1292
3	1	4	5
Total	908	518	1426

The flight profiles also included an exercise code, and were classified according to the amount of oxygen intake as none (00), mild (09–14, 17–20), or heavy (22). These were coded as 1, 2, and 3 respectively. (See Table 3.3). Although the percentage of DCS is almost identical (approx. 63.5%) among subjects performing mild and no exercise, the reader should interpret this table with caution, as other factors like prebreathing times and pressure have been ignored.

Table 3.4 provides a frequency distribution of the different pressure levels and DCS status. As pressure decreases, the percentage of subjects reporting symptoms increases. However, it is very interesting to note that the chance of DCS decreases significantly above the pressure level of 314. There are only 12 cases of DCS among 451 subjects exposed to pressures above 314 mm Hg (2.6 %).

Table 3.5 shows the rate of DCS among subjects with different bubble grades. Among those who did not have any circulating microbubbles, almost 84% did not develop DCS. However, it should be noted that 39% of the people with grade 4 did not exhibit any sign of DCS. It should be emphasized that individuals with high bubble grade could be asymptomatic, while individuals who exhibit symptoms may not show any evidence of bubbles. There was no bubble data available on one individual, so the total sample size here is 1425.

The next section provides a detailed description of the statistical techniques used to model the risk of DCS.

Table 3.4 Classification of PRES by CENSOR

	CENSOR				CENSOR		
PRES (mm Hg)	0	1	Total	PRES (mm Hg)	0	1	Total
141	2	2	4	353	10	0	10
179	11	14	25	378	20	0	20
226	54	97	151	404	192	4	196
231	201	167	368	412	25	0	25
253	37	84	121	429	40	1	41
282	103	86	189	440	10	0	10
297	5	5	10	465	20	1	21
314	56	51	107	493	80	0	80
333	20	2	22	517	9	0	9
350	2	3	5	543	2	0	2
352	9	1	10				
Total					908	518	1426

Table 3.5 Classification of MAXB by CENSOR

	CENSOR		
MAXB	0	1	Total
0	512	96	608
1	54	17	71
2	52	44	96
3	117	92	209
4	172	267	439
Total	907	518	1425

4. Methodology

In this section, we will develop survival models for DCS risk using both parametric and nonparametric methods.

For the parametric model, the survival time (time to onset of DCS) is assumed to have a known probability distribution which depends on a vector of risk factors $\boldsymbol{x}$. The choice of models is limited to those with risk functions that increase initially, reach a maximum, and then decrease. Models satisfying this requirement include the lognormal and loglogistic distributions.

Once the underlying survival distribution is selected, we can describe the likelihood function. The likelihood function L represents the probability distribution of the observed data, and can be expressed in terms of the density and survival functions as

$$L(\theta) = \prod_{i=1}^{M} f(t_i) \quad \prod_{j=1}^{N-M} S(t_j).$$

Here M is the number of uncensored observations, N is the total number of observations in the dataset, and θ is a vector of unknown parameters. The vector includes the parameters for the covariates, as well as location and scale parameters of the underlying survival distribution. Estimates of the parameters in the model are obtained by maximizing the likelihood function, yielding the Maximum Likelihood (ML) estimates. Heuristically, this method provides those estimates of the parameters that are most likely to have generated the observed data. There is usually no closed form solution for this maximization, hence iterative techniques will have to be used to obtain a solution.

The survival function for the lognormal is given by

$$S(t) = 1 - \Phi\ (ln(\lambda t/\sigma)) \qquad \lambda = exp(-\boldsymbol{x}'\boldsymbol{\beta}),$$

where Φ is the cdf for the standard normal distribution, σ is the scale parameter for the normal, and β is the vector of unknown parameters associated with the covariate vector $\boldsymbol{x}$. For the loglogistic distribution, we have

$$S(t) = \frac{1}{1 + (\lambda t)^{\gamma}} \qquad \lambda = exp(-\boldsymbol{x}'\boldsymbol{\beta}),$$

where γ is the reciprocal of the scale parameter. The loglogistic distribution has a very simple form for the survival and risk function as well. The reader is cautioned that the loglogistic distribution has a risk function of the required shape only when γ is less than 1.

The initial attempts at model fitting involved a loglogistic model on three covariates: PRES, BRTALT, EX. Pressure values were transformed to a logarithm scale. The software package SAS was used to obtain the maximum likelihood estimates. The output from the SAS program in Table 4.1 also provides the variance of the estimates and a chi-square value which can be used to determine the relative importance of the different risk factors. Pressure was clearly the most important determinant, followed closely by the proportion of total exposure time spent in prebreathing, and exercise level. The coefficients for all three covariates were highly significant (p-value < 0.001), indicating the importance of these factors in the prediction of DCS risk.

Table 4.1 Parameter estimates from entire dataset

Variable	DF	Estimate	Std. Err.	Chi-sq	p-value
INT	1	-20.23	1.53	173.84	0.0001
PRES	1	4.84	0.28	304.39	0.0001
BRTALT	1	1.98	0.31	40.89	0.0001
EX	1	-0.73	0.13	33.62	0.0001
SCALE	1	0.65	0.02		

A lognormal model was also fit to the data, and the loglikelihoods of the two compared. The predictions from both models were almost identical, providing very little evidence of the superiority of any one distribution. It was therefore decided to use the loglogistic model in all further analyses because of its' simpler form.

The next step in the analyses was to examine the effects of interactions between the various risk factors. Interactions between the main factors like pressure and exercise, pressure and prebreathing times, and exercise and prebreathing times were all included in the analysis. This did not result in a significant change in the loglikelihood values. The interactions also tended to mask the effects of the main

factors, and did not provide much improvement in the predictions. This confirmed the belief that these three primary risk factors were sufficient to adequately predict the probability/ risk of DCS.

To examine the predictions from this model, (henceforth referred to as Model 1), we selected a flight profile from the database for which sufficient data was available. This profile had PRES = 231, BR = 135, TALT = 240, and EX = 2 (Mild). The empirical or observed cdf for this profile is obtained using the Kaplan-Meier (KM) method [9]. The points in the graph represent only individuals who had DCS. Figure 4.1 displays the observed and estimated cdf for this profile. The two graphs are fairly close initially (up to 90 minutes), but the fitted model tends to under predict the probability of DCS at later times. For example, the model predicts the chance of DCS occurring within 150 minutes to be 25 %. From the data, 32 % of individuals experience DCS within this time frame.

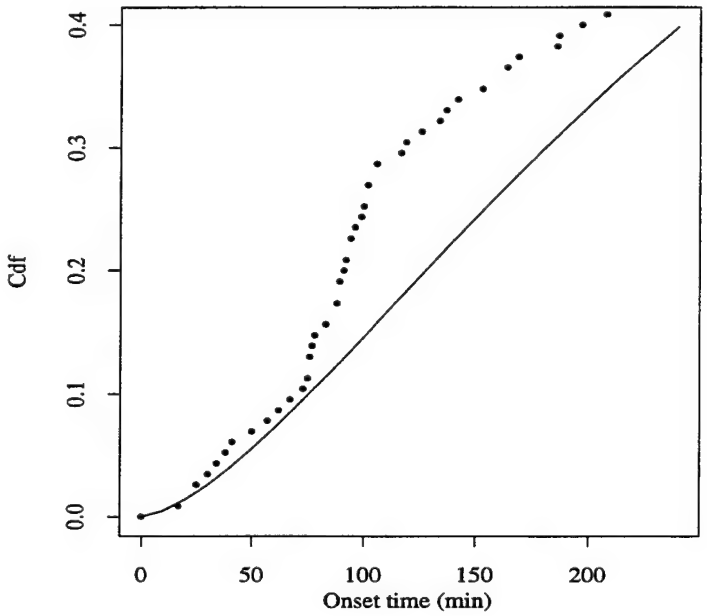


Figure 4.1 Observed and Estimated Cdf: Model 1

Similar trends were observed for several other profiles. The model tends

to be rather conservative when predicting the DCS probability for longer exposure intervals. Such low predictions could be extremely hazardous in real life situations where protocols call for extended periods of exposure. In these kinds of applications, a model which over predicts/ exaggerates the risk slightly is definitely preferable in the long run.

The concerns raised above led us to examine the database more carefully in the hope of explaining this apparent anomaly. From the cross tabulation tables presented in the data management section, almost 50 % of individuals exposed to pressures up to and including 314 mm Hg (altitudes above 22,500 ft.) had DCS. For high pressures (low altitudes) the risk is significantly lower. Only 12 of 451 individuals exposed to pressure levels above 314 mm Hg had DCS. These records could be the reason for the consistent low predictions from Model 1. It was decided to fit a loglogistic model with the same three covariates to a subset of the data, individuals exposed to low pressures levels ($\leq$ 314 mm Hg). This subset contained 975 datapoints, with a DCS rate of 48 %.

Table 4.2 provides the estimates and standard errors for the loglogistic model (Model 2). All three covariates remain highly significant, so do their contributions to the model. Clearly, the effect of pressure has diminished, the three covariates now contributing almost equally to the model. This is quite different from the earlier model, where the effect of pressure was much more pronounced.

Table 4.2 Parameter estimates from reduced dataset

Variable	DF	Estimate	Std. Err.	Chi-sq	p-value
INT	1	-8.10	1.99	16.55	0.0001
PRES	1	2.59	0.36	52.32	0.0001
BRTALT	1	1.79	0.31	34.52	0.0001
EX	1	-0.65	0.12	29.38	0.0001
SCALE	1	0.64	0.02		

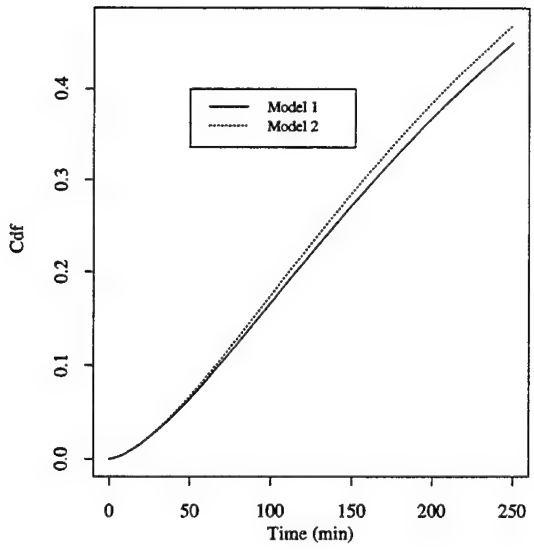
We now compare the predictions from the two models for different profiles (Figure 4.2). For a pressure of 231 mm Hg and high prebreathing time, the two models

provide almost identical predictions (Figure 4.2a) .When the pressure is increased to 282 mm Hg with a lower prebreathing time, the difference increases with Model 2 providing higher predictions (Figure 4.2b). The same trend is observed when the pressure increases to 314 mm Hg with 0 prebreathing (Figure 4.2c). Clearly, Model 2 provides a higher DCS probability which is more in tune with empirical evidence. The last graph (Figure 4.2d) has a pressure level of 404 mm Hg and prebreathing time of 60 minutes. Model 2 again provides higher predictions. However, for such low altitudes and moderate prebreathing times, the observed rate of DCS is extremely small. Under these circumstances, it would not be unreasonable to use Model 1 for prediction. It seems a logical progression to fit a model to the remainder of the dataset (above 314 mm Hg) and use it for low altitude predictions. However, the paucity of symptomatic individuals at these altitudes makes model fitting and validity questionable.

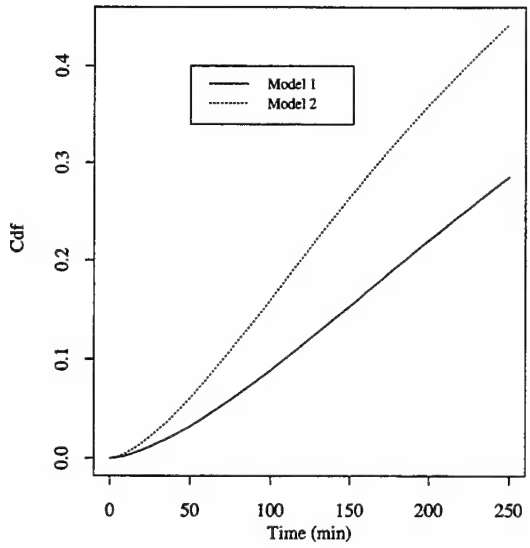
4.1 Model Validation

In this section, we evaluate the performance of the fitted model using validation and cross validation methods. These procedures would allow us to examine the discrepancies in the predictions and might suggest improvements that lead to a better model. The first step in this exploratory process was to obtain the estimated cdf for two flight profiles with PRES = 231 mm Hg, EX = Mild, TALT = 240 min, and BR = 135 min , 75 min. The graphs (not shown) suggest a close agreement between the estimated cdf and the empirical data.

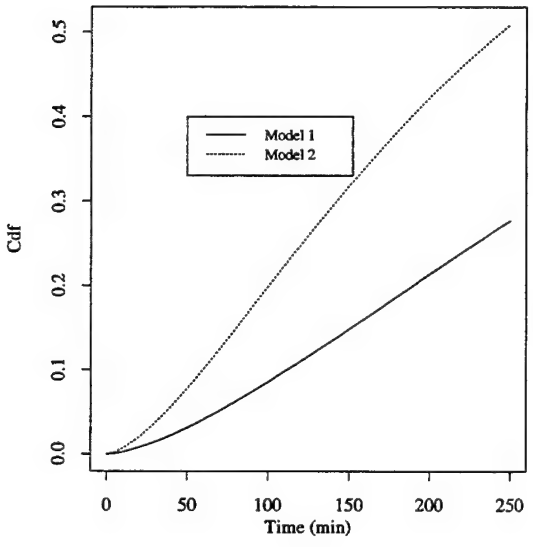
This was certainly a step in the right direction. However, one of the main purposes of model fitting is to use the model for extrapolation, predicting the chance of DCS for flight profiles that have not been tested. To this end, all individuals in the above profiles were deleted from the database, and the loglogistic model fit to the remainder of the data points. An overlay of the estimated cdf from this truncated dataset and the observed onset times provides a cross validation of the model (Figure 4.3). For a prebreathing time of 135 minutes, Figure 4.3b clearly shows the lack of fit and indicates a need for further modifications to enhance the predictive power. These problems will be addressed in detail in the next section.



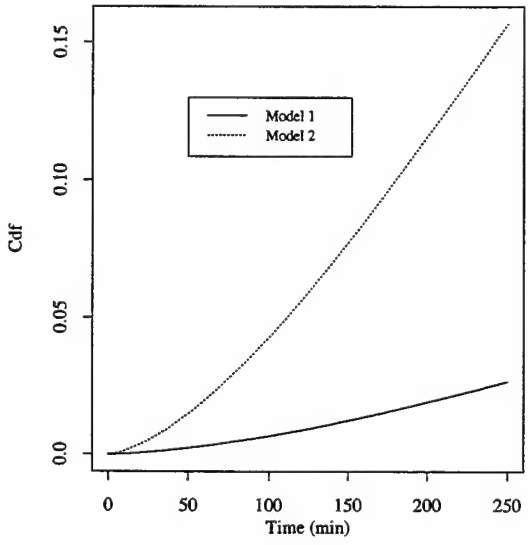
(a) PRES = 231 mm Hg, BR = 120 min



(b) PRES = 282 mm Hg, BR = 60 min

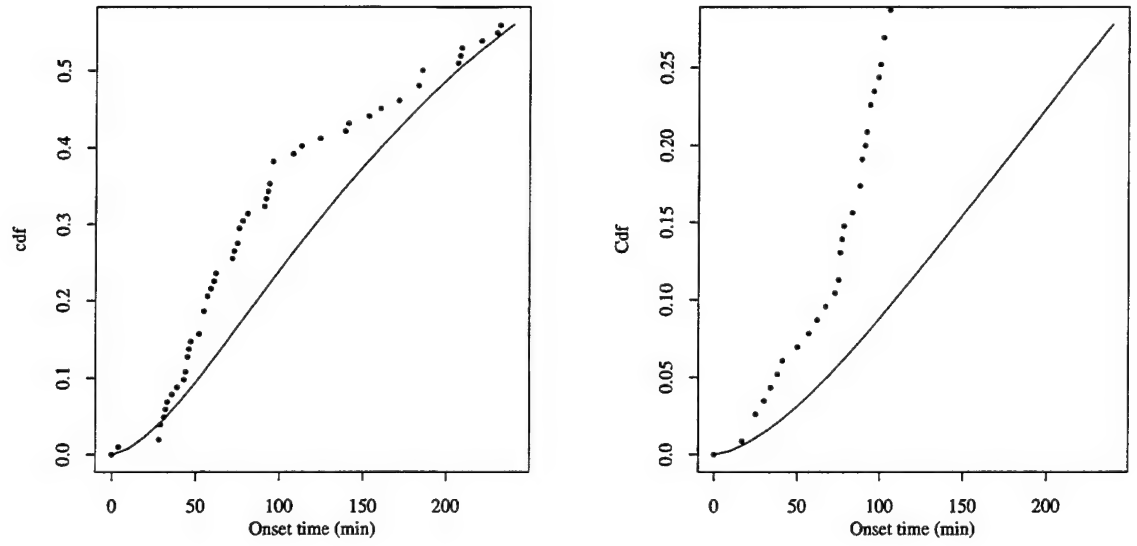


(c) PRES = 314 mm Hg, BR = 0 min



(d) PRES = 404 mm Hg, BR = 60 min

Figure 4.2 Predictions from Models 1 and 2



(a) BR = 75 min

(b) BR = 135 min

Figure 4.3: Cross Validation (Model 2): PRES = 231 mm Hg, TALT = 240 min, EX = Mild

4.2 Survival Model with Weights

A significant cause for lack of fit is the large variation in the exposure times. This consequently creates large dispersion in the onset times for different flight profiles, and results in the failure of one model to adequately predict DCS risk for all flight profiles. A simplistic approach is to fit separate models for individual profiles. This would clearly provide no solution to the main objective of predicting the probability of DCS for future protocols.

For flights of shorter durations the dispersion in the onset times for individuals experiencing DCS is fairly small. However, for longer flight durations, the dispersion is clearly larger. Prebreathing times also play a part in this variability because higher prebreathing times reduce the incidences of DCS. This nonhomogeneity can be controlled through transformations of the data or the assignment of appro-

priate weights to the individual observations. We will use the second approach, and attempt to determine the weights from the data after a careful examination of the underlying factors.

The data on symptomatic individuals was divided into several groups after studying the cross classification tables. The first group included individuals with TALT < 181 minutes (23 individuals). The second group consisted of individuals with TALT of 240 minutes and prebreathing times greater than 75 minutes (56 individuals). Individuals with prebreathing times ≤ 75 minutes constituted group three (199 individuals). The fourth group included all individuals with TALT above 240 minutes (228 subjects). Group five contained all the censored individuals (469).

We computed the standard deviations of the onset times in these groups. Group 1 had the smallest standard deviation and was assigned the base weight of one. The other weights were determined by the ratio of their standard deviations to that of the base group. The higher the standard deviation, the lower the weight assigned to that group. The weights for the various groups are displayed in the table below.

Table 4.3 Standard deviations and weights

Group	TALT (min)	BR (min)	St. Dev	Weight
I	≤ 180	≥ 0	38.53	1.00
II	240	> 75	63.20	0.61
III	240	≤ 75	67.87	0.57
IV	> 240	≥ 0	80.76	0.48
V			89.41	0.43

After determining the appropriate weights, the likelihood function was modified to

$$L(\theta) = \prod_{i=1}^{M} [f(t_i)]^{w_i} \prod_{j=1}^{N-M} [S(t_j)]^{w_j},$$

where w_i is the weight assigned to the i-th observation. The loglogistic model was fit to the 975 observations using the above weights. The loglikelihood value obtained was -560.84, much lower than the corresponding value for the unweighted model. Table

Table 4.4 Parameter estimates for the weighted model

Variable	DF	Estimate	Std. Err.	Chi-sq	p-value
INT	1	-8.00	2.45	10.63	0.0011
PRES	1	2.53	0.44	32.57	0.0001
BRTALT	1	1.29	0.39	11.26	0.0008
EX	1	-0.53	0.14	13.68	0.0002
SCALE	1	0.60	0.03		

4.4 provides the estimates for this weighted model. Pressure again had the largest contribution, followed by the other two covariates.

The cross validation was repeated for this model using the flight profile with BR = 135 min. The weights were recalculated after deleting observations belonging to this specific profile. The improvement in the predictions are clearly dramatic (Figure 4.4). There is a very close agreement between the estimated probability of DCS and the observed cdf. This trend was visible for several other profiles as well.

Figure 4.5 shows the predicted and observed cdf's for the flight profile with BR = 75 min. This predicted model is caluclated from the entire dataset to examine how well the model fits the underlying data. Based on these observations, this model though simple, provides extremely good predictions.

These validations and cross validations confirm our beliefs that this model does indeed describe the nature of DCS and can provide very accurate predictions. We would now like to determine the effects of the different covariates on the DCS probability/ risk (Figure 4.6).

Figure 4.6a shows the probability of DCS for prebreathing times 0, 60 and 90 minutes. As prebreathing time increases, the chances of DCS decrease. The decrease is significant when we move from 0 prebreathing to 60 minutes of prebreathing. The difference is not that marked when we move from 60 to 90 minutes of prebreathing. Figure 4.6b examines the effects of exercise. As exercise levels move from rest to mild to heavy, the probability of DCS increases by approximately the same amount. The effects of pressure change on the probability of DCS are seen in Figure 4.6c. As pressure increases form 226 mm Hg to 314 mm Hg, the chances of DCS decrease.

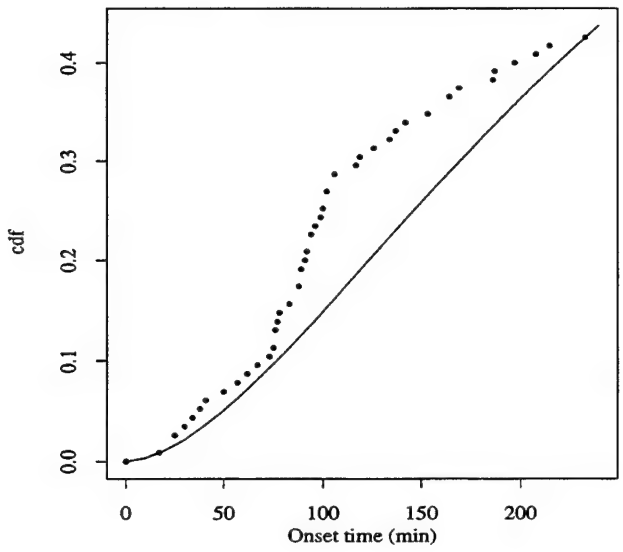


Figure 4.4 Cross Validation (Weighted Model): BR = 135 min

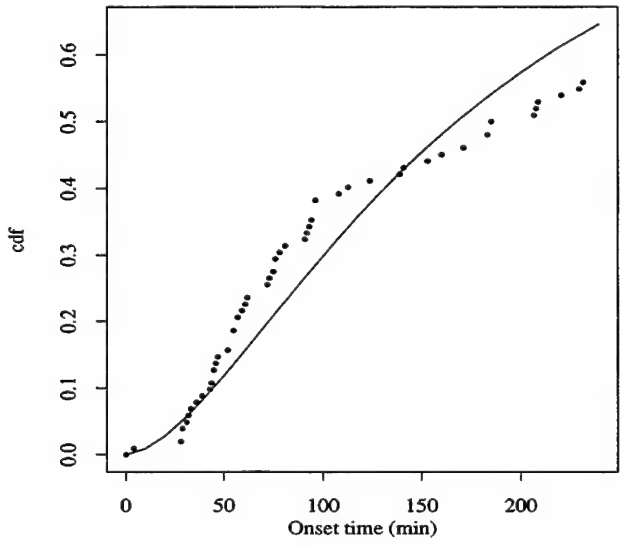


Figure 4.5 Validation (Weighted Model): BR = 75 min

Table 4.5 Median onset times

PRES (mm Hg)	TALT (min)	EX	BR (min)	MED
226	240	2	15	114.5
			60	146.1
			90	171.8
226	240	3	15	67.4
			60	85.9
			90	101.1

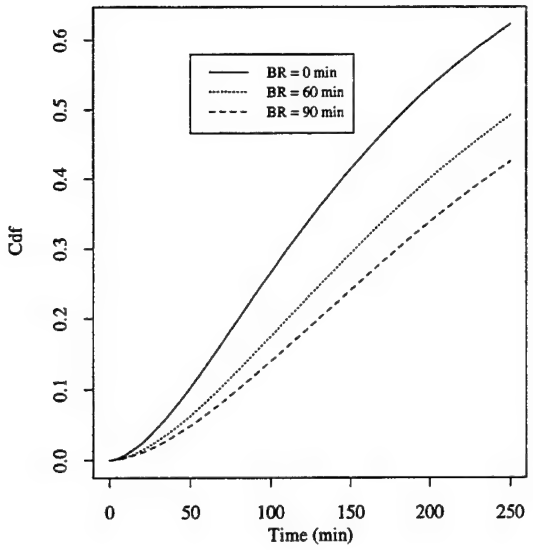
Figure 4.7 provides the corresponding risk functions for the three prebreathing times. The risk is clearly highest for 0 prebreathing.

We also provide a table of the median survival time for different profiles. The median survival time is the time by which 50 % of individuals are expected to experience DCS symptoms, and provides a way of assessing the effects of prebreathing times and exercise. From the table, we can see that for fixed pressure, time at altitude, and exercise, individuals who prebreathe more have a longer median survival time. The trends are similar for exercise: individuals who perform heavy exercise have shorter median survival times than individuals performing mild exercise. It is possible for the median survival time to be greater than the time of exposure, because of the large number of censored individuals. For the loglogistic distribution the median(M) has a particularly simple form given by

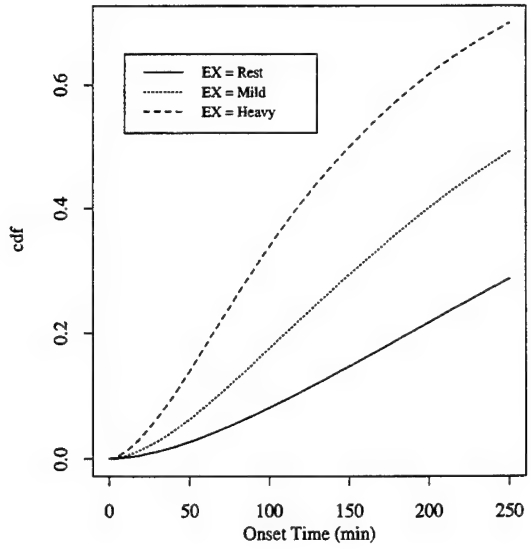
$$M = 1/\lambda, \qquad \lambda = exp(-\boldsymbol{x}'\boldsymbol{\beta}).$$

4.3 Nonparametric Methods: Cox's Proportional Hazard Model

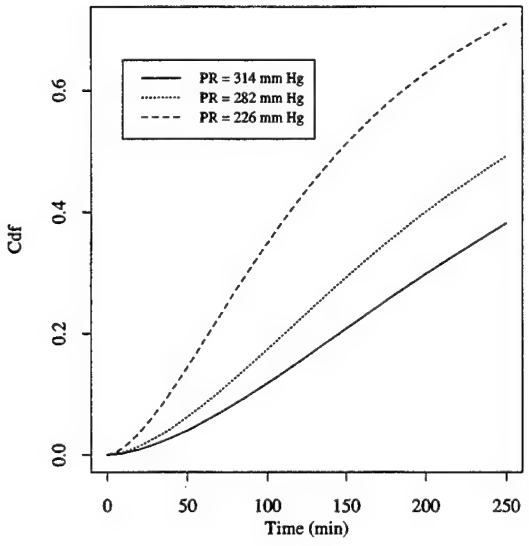
In this section we fit a nonparametric model, Cox's proportional hazards model to the data. The model assumes that the risk functions for two individuals differing only in the level for one factor are proportional to each other. As an example, the risk functions for individuals with and without exercise are parallel curves. The estimates are provided in Table 4.6.



(a)



(b)



(c)

Figure 4.6 Predicted Cdfs for the Weighted Model

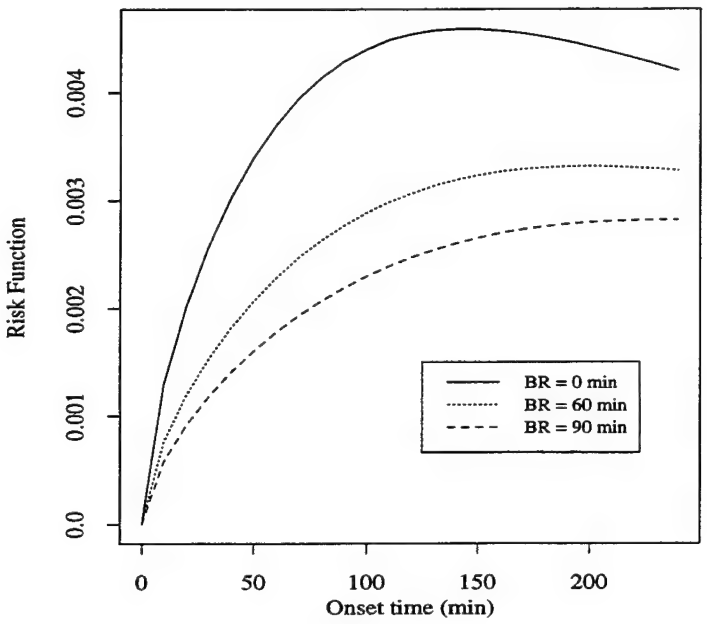


Figure 4.7: Predicted Risk Function (Weighted Model): PRES = 282 mm Hg, TALT = 240 min, EX = Mild

Table 4.6 Estimates for Cox's PH Model

Variable	Estimate	Std. Err.	Chi-sq	p-value	Risk-ratio
PRES	-2.75	0.42	42.61	0.0001	0.064
BRTALT	-2.22	0.37	36.67	0.0001	0.109
EX	0.72	0.15	24.66	0.0001	2.066

The risk ratios in the last column have a practical interpretation. For example, the risk of DCS for individuals who perform mild exercise is 100 (2.066-1) % higher, (i.e., almost double) compared to individuals at rest.

In order to compare the parametric and nonparametric models, we plotted the estimated cdf for the profile: PRES = 282 mm Hg, TALT = 240 min, EX = Mild. The curves for prebreathing times 0, 60 and 90 minutes are given in Figure 4.8. The nonparametric graphs are not smooth because they use the original data points and there are a few large onset times which tend to pull the graph upward. The parametric and nonparametric estimates of the cdf (Fig 8 anf Fig 4.6 (a))are almost identical for 0 prebreathing. For 60 and 90 minutes, the nonparametric graphs tend to have lower predictions. The close agreement between the two methods was encouraging. Based on the ease of dealing with parametric models, we believe that the loglogistic model is most suitable for DCS modeling.

4.4 Loglogistic Models for Time of onset of bubbles

The experiments conducted at the Armstrong Laboratory also included measurements on bubbles. A Doppler ultrasound was used to determine the density of bubbles at fifteen minute intervals. The bubbles were graded on a Spencer scale with values ranging from 1 (low) to 4 (high). From this data, the time at which the bubble grade is maximum was extracted along with the corresponding grade. The subjective nature of bubble grade data, led to the following classification for the statistical analysis: Bubbles were classified as grade low (grades 0,1) or high (grades 2,3 and 4).

Since bubble grade, and onset times of bubbles are key factors in the prediction of DCS risks, it was decided to construct approporiate models for these variables. A logistic model was fit to the probability of low and high grades. This probability depends on the time of exposure, prebreathing time, and exercise status. Pressure was found to not have a significant effect on this probability in the presence of these other variables. The logistic model helped to identify those profiles for which high grades were more likely to occur compared to low grades. In general, it was found that subjects who performed mild exercise in flights of moderate/long duration (240 minutes or longer) were more likely to have high bubble grades. For individuals at rest with low prebreathing times, high grades were observed. If prebreathing times

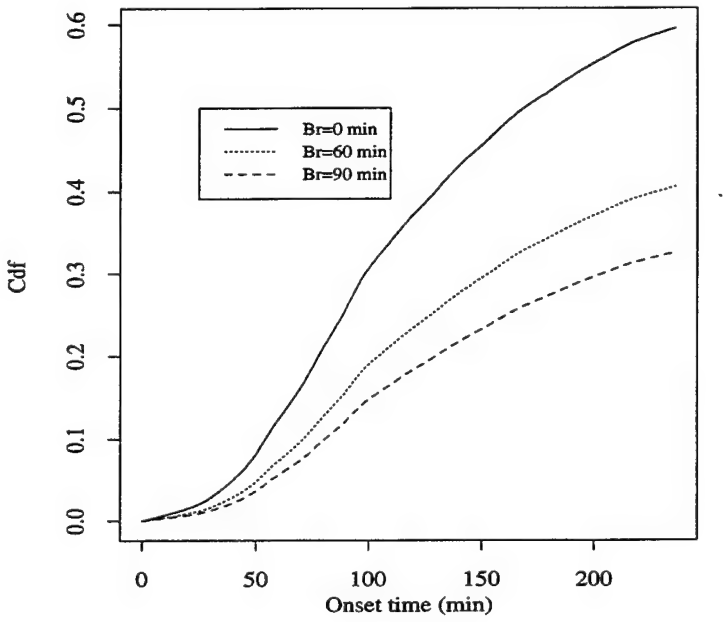


Figure 4.8: Predicted Cdf: Cox's Model: PRES = 282 mm Hg, TALT = 240 min, EX = Mild

Table 4.7 Percentiles of MAXT (PRES = 282 mm Hg, EX = Mild)

	Percentile		
BR (min)	25	50	75
0	46.7	69.4	103.0
60	69.3	102.9	152.9
90	72.0	106.9	158.9

were moderate or high, the individuals almost always had very low bubble grades.

The time at which the maximum grade is attained could be interpreted as a 'survival time' and modeled accordingly. Clearly this time is affected by the amount of prebreathing time, exercise status, and pressure. The risk function increases steadily, reaches a maximum, and then decreases because of denitrogenation. Once again, loglogistic and lognormal models are found to be appropriate. The models are fit to only those individuals who had high bubble grades. The loglogistic model provides information on the chance of observing high bubble grades within a specified time period as a function of several risk factors. This model can be used to determine the percentiles for MAXT. In particular, the median will represent the time by which 50 % of individuals will have high bubble grades. This model provides an "estimate" of the time at which the bubble grade is maximum. Table 4.7 provides the 25th, 50th, and 75th percentiles for a flight profile with PRES = 282 mm Hg, and EX = 2 (Mild). From the table, we observe that 25 % of individuals with no prebreathing will have high bubble grades within 47 minutes, this interval increases to 69 minutes with 60 minutes of prebreathing.

The next step is to assimilate this information on the time of onset of maximum bubble grade into a model for predicting DCS risk. The covariate MAXT was added to the loglogistic model. The EX covariate was found to be nonsignificant in this model. However, exercise is still a part of the predictions because it has an effect on MAXT. The model was fit for the two grade categories:high and low. For low bubble grades, as expected, the effect of MAXT was negligible. However, from table 4.8, it is clear that MAXT has a tremendous effect on the risk of DCS for high bubble

Table 4.8 Parameter estimates:weighted model (bubble data for grades 3 and 4)

Variable	DF	Estimate	Std. Err.	Chi-sq	p-value
INT	1	-3.66	1.80	4.12	0.0424
PRES	1	1.34	0.31	17.37	0.0001
BRTALT	1	0.96	0.30	10.21	0.0014
MAXT	1	0.01	0.00	183.58	0.0001
SCALE	1	0.37	0.02		

grades. It dampens the effect of all the other covariates. This seems intuitive because MAXT does depend on these covariates. Since the primary focus of this investigation is prediction of DCS for varying flight profiles, input values for the MAXT variable are necessary. One option is to use the median or 75th percentile as an input in the model. The 75th percentile provides a conservative estimate since the models for bubble times only use individuals with recorded bubbles.

Figure 4.9 shows the effect MAXT has on the predictions. If MAXT is low (25th percentile), the curve rises very quickly. However, if the value of MAXT is high, the curve is less steep. The points scattered in the plot represent the observed probabilities. All three choices of MAXT provide very close estimates at 240 minutes ranging from 78 % to about 85 %. For the same profile, the model without bubbles predicted the final probability to be 60 %. There is a remarkable improvement with the addition of bubble data.

An alternative route to obtaining inputs for MAXT is to use information from the bubble growth model currently being developed at the Armstrong Laboratory.

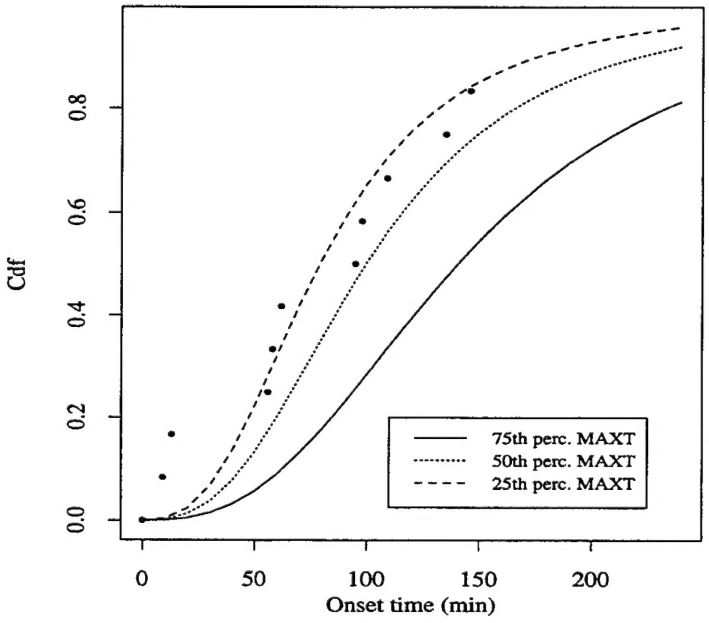


Figure 4.9: Predicted Cdf: PRES = 282 mm Hg, TALT = 240 min, EX = Mild, BR = 0 min

5. Conclusions

This report has discussed the modeling of DCS data using survival analysis techniques. Different models were constructed to predict the probability of DCS over time using both parametric and nonparametric methods. The predictions from the model for different profiles agreed quite closely with empirical data available in the database. Modifications to the model were made using weighted estimates, which helped to significantly improve the predictions. Validation and cross validation techniques were used to evaluate the goodness of fit of these models. Models incorporating bubble data were also developed. We believe that any further research in the area of DCS modeling should incorporate both the statistical and mathematical aspects of the data.

References

[1] H. D. Van Liew, J. Conkin, and M. E. Burkard, "Probabilistic model of altitude decompression sickness based on mechanistic premises," *Journal of Applied Physiology*, vol. 76, pp. 2726–2734, 1994.

[2] W. A. Gerth and R. D. Vann, "Statistical bubble dynamics algorithms for assessment of altitude decompression sickness incidence," tech. rep., Armstrong Laboratory, 1995.

[3] K. Kumar, B. Waligora, and D. Calkins, "Threshold altitude reuslting in decompression sickness," *Aviation, Space, and Environmental Medicine*, vol. 61, pp. 685–689, 1990.

[4] K. Kumar, D. S. Calkins, J. Waligora, J. Gilbert III, and M. Powell, "Time to detection of circulating microbubbles as a risk factor for symptoms of altitude decompression sickness," *Aviation, Space, and Environmental Medicine*, vol. 63, pp. 961–964, 1992.

[5] K. Kumar and M. Powell, "Survivorship models for estimating the risk of decompression sickness," *Aviation, Space, and Environmental Medicine*, vol. 65, pp. 661–665, 1994.

[6] J. Conkin, K. Kumar, M. Powell, P. Foster, and J. Waligora, "A probabilistic model of hypobaric decompression sickness based on 66 chamber tests," *Aviation, Space, and Environmental Medicine*, vol. 67, pp. 001–008, 1996.

[7] D. R. Cox, "Regression models and life tables," *Journal of the Royal Statistical Society B*, vol. 34, pp. 187–202, 1972.

[8] E. T. Lee, *Statistical Methods for Survival Data Analysis.* Wiley, New York, 1992.

[9] J. F. Lawless, *Statistical Methods for Survival Data Analysis.* Wiley, New York, 1982.